REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

A. Claims 1-3, 5 and 12-27 have been finally rejected. Claims 6, 28 and 29 are in withdrawn status.

In order to expedite prosecution, claims 1, 28 and 29 have been amended to refer to buprenorphine instead of "an opioid analgesic from the phenanthrene group" (claim 12 is now superfluous and has been cancelled). Claim 23 is dependent upon claim 6 which is in withdrawn status and therefore, claim 23 should also be in withdrawn status. Claim 24 is dependent upon claim 8 which was previously cancelled and as such claim 24 has been cancelled. New claim 30 reintroduces the element cancelled from amended claim 22.

Therefore, the proper status of the claims under examination after this amendment prior to consideration of the applicants arguments below is that claims 1-3, 5, 13-22, 25-27 and 30 have been rejected and claims 6, 23, 28 and 29 are in withdrawn status.

No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

B. As there has been no indication that the restriction/election of species has been withdrawn or that the scope of the examination was expanded beyond the applicants' elected species, the invention was presumed to be examined for the election wherein:

1. The patch is a matrix-type patch
2. The adhesive is a synthetic rubber which in turn is comprised of styrene-butadiene-styrene block copolymer
3. The another penetration enhancer is an N-methyl pyrrolidone
4. The preservative is an organic acid
5. The backing comprises of polyester.

As such, by virtue of the restriction/election of species requirement, this election was deemed to be patentably distinct from other elections which could have been made by the applicants.

II. THE 35 U.S.C. 112, 2nd PARAGRAPH REJECTION HAS BEEN OVERCOME

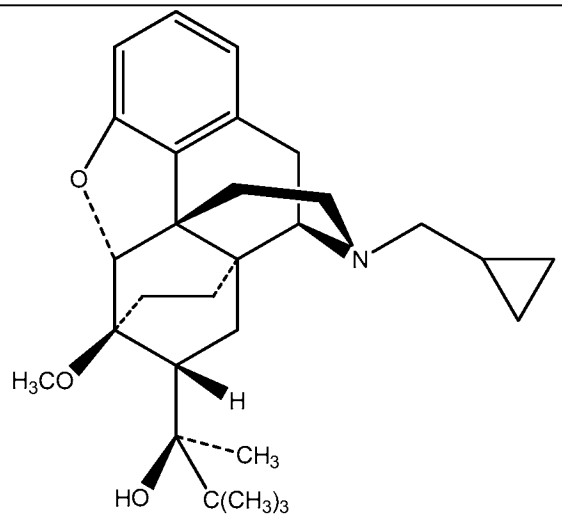
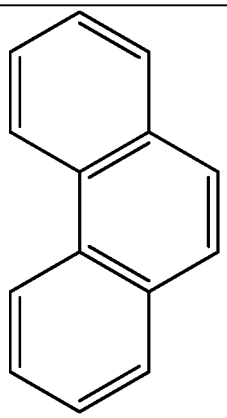
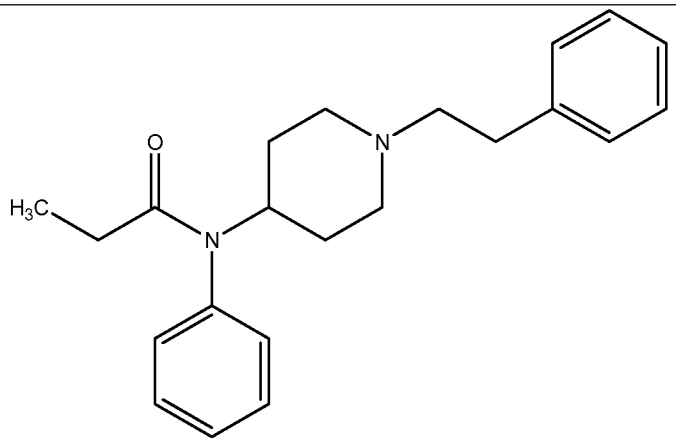
The rejection of claims 22 and 24 have been addressed by the amendment to claim 22 and the cancellation of claim 24; new claim 30 has been added to present the range removed from claim 22.

III. THE 35 U.S.C. 102(e) REJECTION HAS BEEN OVERCOME

Claims 1-3, 5, 12-17, 26 and 27 were rejected as allegedly being anticipated over Tisa-Bostedt et al. (U.S. Patent Application Publication 2004-0001882 - "Tisa-Bostedt") as evidenced by Cote et al. (U.S. Patent Application Publication 2009-0209571 - "Cote").

Establishing anticipation requires that each element of the applicants' invention is taught and that the identical invention is shown in as complete detail as is contained in the claim. *See MPEP 2131*. However, Tisa-Bostedt does not meet this standard for establishing anticipation.

The applicants' claims as considered during examination were directed toward an "an opioid analgesic from the phenanthrene group" (which encompasses buprenorphine). However, an opioid analgesic from the phenanthrene group does not encompass the use of fentanyl in Tisa-Bostedt as asserted in the Office Action (compare the structures of buprenorphine and fentanyl):

Buprenorphine	Phenanthrene ring
	
Fentanyl	
	

The reliance on Cote is not well understood as (1) Cote does not qualify as prior art under 102 as the earliest priority date that can be established in **18 May 2006**, whereas the present application is a National Stage application of PCT/EP04/08346 filed in English on **26 July 2004**; and (2) paragraph [0052] from Cote relied upon by the Examiner merely teaches that fentanyl and buprenorphine are opioid analgesics; as can be seen from the above structure, fentanyl is NOT an opioid analgesic from the phenanthrene group.

As all elements of the applicants' claims have not been taught, Tisa-Bostedt alone or in combination with Cote does not anticipate the applicants' claimed invention for this reason alone.

In addition, Tisa-Bostedt does not teach the identical invention in as complete detail as is contained in the applicants' claim which as amended require as little as buprenorphine, a synthetic rubber adhesive of a styrene-butadiene-styrene block copolymer and an aloe composition as transdermal penetration agent. In contrast, not only does Tisa-Bostedt refer to the wrong active ingredient, release of the active ingredient is not based on aloe composition as transdermal penetration agent, but rather the concentration ratio between aloe vera extract and resin (see page 2, paragraph [0056] of Tisa-Bostedt)

IV. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

Preliminary note:

The applicants note that even though the Examiner elected to present new combinations of references to try and establish obviousness, determinations of obviousness still require consideration of the claims as a whole and consideration of all the arguments and evidence which are present in the record.

The applicants had previously made assertions of unexpected results which were supported by the declarations by Dr. Elisabeth Myers signed on 26 August 2009. There is not indication from any of the three obviousness rejections cited below that the applicants' assertions and declarative evidence were considered when formulating the obviousness rejection.

As such, since there nothing which contests the applicants' assertions of unexpected results, the applicants claimed are unobvious over the rejections made below for this reason alone.

The applicants present their earlier assertions of unexpected results in the quoted passage below:

> "When considering the applicants invention as a whole, the present invention provides a solution for the problem of imparting a pharmaceutical formulation with properties which enable an opiod analgesic to be transdermally administered. The solution for this problem consists in
> - a transdermal formulation comprising
> - a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer,
> - an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and
> - an aloe composition as transdermal penetration agent.
>
> With respect to amended claim 1, the formulation comprises a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer.

The inventors have carried out comparative experiments which are similar to Example 1 in the specification and which are now presented for the first time with this submission in the Declaration by Dr. Elisabeth Meyer.

In Example 1 of the description of the present application experiments with different matrix patches are presented. The results are summarized in Table I on page 16 of the description. A matrix patch is provided which comprises a mixture of buprenorphine (the analgesic), an aloe (the transdermal penetration agent) and a styrene-butadiene-styrene polymer (the adhesive). Flux experiments with hairless mouse skin reveal buprenorphine fluxes in the range from 0.8 to 2.3 $\mu g/cm^2*h$ and the transdermal penetration effect of aloe compositions.

In the comparative experiments the styrene-butadiene-styrene polymer (the adhesive) was replaced by several acrylate adhesives, i.e. the adhesive which is disclosed by Fischer as the usual adhesive in combination with the intradermal penetration agent (the aloe composition) and the drug.

The results as disclosed in the description and the results of the comparative experiments are presented in the following table below (see next page):

Adhesive type	PSA	Buprenorphine (% w/w)	*Aloe vera* (% w/w)	Flux (hairless mouse skin)	**Formation of crystals**
Examples of the Present Invention (cf. Table I of the invention, page 16)					
Styrene-butadiene-styrene polymer	DT 6173	15	20	2.3 μg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	5	20	0.8 μg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	10	10	0.9 μg/(cm^2*h)	–
Comparative Examples					
Acrylate-vinylacetate with carboxy groups	DT 2825	10	10	1.1 μg/(cm^2*h)	+
Acrylate-vinylacetate with hydroxyl groups	DT 2287	10	10	1.1 μg/(cm^2*h)	+
Acrylate with functional hydroxy groups	DT 2510	10	10	1.3 μg/(cm^2*h)	+
Acrylate-vinylacetate without functional groups	DT 4098	10	10	1.5 μg/(cm^2*h)	+

It should first be noted that in the description of the present application the fluxes are accidentally given as g/(cm^2*h). In fact, also in the case of the invention the fluxes are in the micro gram range and should read as μg/(cm^2*h) which is corrected in the specification.

When comparing the results of the above experiments in which the patches comprise 10 % (w/w) *Aloe vera* it turns out that the fluxes which are obtained with the styrene-butadiene-styrene polymers as adhesive (according to the invention) and with the acrylates as adhesives (comparative examples) are similar. ***However, with the acrylate polymers a disadvantageous crystallization of the drug (buprenorphine) in the matrix is observed over the time.*** Such a crystallization reduces the long term stability of the formulations and the amount of drug available for the transdermal penetration is very disadvantageous for transdermal applications, for which a relatively high concentration of the dissolved drug in the pharmaceutical formulation is needed. This disadvantageous crystallization effect can be avoided using the styrene-butadiene-styrene polymers of the invention.

The Fischer invention does not comprise any hint that, different from acrylates, styrene-butadiene-styrene polymer adhesives in pharmaceutical formulations can prevent crystallization of the drug, whereby the long term stability of formulations comprising buprenorphine and an aloe composition are

improved and whereby the formulations may be used as transdermal formulations."

A. Claims 1-3, 5, 12-22 and 25-27 were rejected as allegedly being obvious Tisa-Bostedt et al. (U.S. Patent Application Publication 2004-0001882) in view of Fischer et al. (U.S. Patent 6,455,066 - "Fischer").

As noted above, Tisa-Bostedt does not teach all aspects of the applicants' claimed invention at least for the reason that fentanyl is not buprenorphrine.

To the extent that the Examiner is arguing that buprenorphrine is obvious variant of fentanyl, the applicants again refer to the structures provided above on page 7 of this response.

Moreover, not only does buprenorphine have a completely different structure than fentanyl, the physicochemical properties of the respective compounds are also different:

Property	Buprenorphine	Fentanyl
M.W.	467.64	336.47
Partition coefficient in octanol-water	1217	860
Solubility	Little to no solubility in water (lipophilic)	Soluble in water and fat

The increased size and partition coefficient and differences in solubility pose different problems for buprenorphine than for fentanyl especially when making these considerations in the context of transdermal delivery.

The continued reliance on Fischer as a supporting reference is baffling to the applicants as it has previous been shown that there is a difference between transdermal and intradermal compositions which has never been adequately addressed (the applicants supply a copy of their earlier arguments on this point in quotations below):

> "First, the applicants' invention is directed toward a ***transdermal*** formulation whereas the invention of Fischer is directed toward an ***intradermal*** composition. The differences in administration is well known in the art and is even addressed by Fischer themselves in the background of their invention (see col. 1, lines 39-48).[1] As one of ordinary skill in the art would recognize that

[1] "In general, drug administration via the skin is divided into two categories: 1) ***transdermal*** administration and 2) ***intradermal*** administration. Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases. One the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmocological effects of the drug localized to the intracutaneous regions of drug penetration and deposition. ***Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.***" (emphasis added)

intradermal administration is intended to ***avoid*** any transdermal absorption, the Fischer reference would not be readable upon or suggestive of the applicants' transdermal formulation.

Second, Fischer is directed toward the delivery of an ***anesthetic*** whereas the applicants' transdermal formulation is directed toward delivery of an ***opioid analgesic*** from the phenanthrene group which is consistent with their disclosed methods of delivery, i.e. Fischer wants localized delivery of their anesthetic and to avoid systemic delivery whereas the applicants' invention wants to provide systemic delivery to maximize the pain relief associated with the opioid analgesic…

The arguments presented in the final rejection appeared to concede that there are differences between intradermal and transdermal delivery.[2] The final rejection stated that:

"The Applicant's claim uses the same delivery system; therefore, for the drugs to be delivery (sic) from the skin to the inside of the skin, then ***the drugs would have to be transdermally delivered, then intradermally delivered***." (page 4, lines 3-5 of the final rejection (emphasis added))

However, this analysis is incorrect and appears to confuse the definition of intradermal and transdermal administration.

Intradermal administration is the transportation of a drug into the skin, more specifically, into the dermis, **without the uptake into the venules and arterioles**, which only populate the deeper layers of the skin, i.e. the hypodermis. See page 145 from *Concepts of Human Anatomy and Physiology*, Wm. C. Brown Publishers, (1992) which is attached to this response which includes a diagram of the integumentary system (skin).

In other words, the drug penetrates from the vehicle (e.g. in a patch) through the *Stratum corneum* into the epidermis and possibly into the dermis, however without reaching the capillaries and the blood stream in a pharmacologically relevant amount. Intradermal administration thus serves for the topical administration of a drug which should be effective in the skin. An example for these drugs are anesthetics. Intradermal administration is intended to impart a cutaneous effect. Intradermal absorption occurs with little or no systemic absorption.

In contrast, **transdermal administration** includes necessarily all of the above described aspects of intradermal administration. However, in the case of

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[2] The applicants attach to this response further evidence of the differences between intradermal and transdermal delivery from Allen et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (8th Edition)*, pages 298 and 448, (2005). – "Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances ***through the skin*** and ***into the general circulation for their systemic effects***. pg. 298 (emphasis added). "A number of substances may be effectively injected into the corium [the dermis], the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, ***desensitization***, or immunization." pg. 448 (emphasis added).

> transdermal administration, the further transportation of the drug in the vicinity of the capillaries and the uptake of the drug by the blood capillaries are desired, i.e. into the hypodermis. An example for these drugs are analgesics. Transdermal administration is intended to impart a systemic effect. Transdermal absorption occurs predominantely with systemic absorption into the arterioles and venules, after the absorption into the skin has occurred.
>
> Therefore, the Examiner's statement is factually incorrect as intradermal administration does NOT occur after transdermal delivery. Intradermal administration speaks to an administration method which is different and distinct from transdermal administration and is even recognized as such within the Fischer reference (see again col. 1, lines 39-48)."

Moreover, Fischer ***teaches away*** from any assertion of equivalence between fentanyl and burprenorphine as Fischer recognized that the behavior of a penetration enhancer is strongly dependent on the drug (see col. 2, lines 35-41) and as such one of ordinary skill in the art would not impute the penetration activity of aloe vera with an anesthetic (or an opioid analgesic which is not from the phenanthrene group such as fentanyl) as being predictive of the activity with an opioid analgesic of the phenanthrene group (e.g. buprenorphine) and in this instance, it is uncertain what relevance of such predictability would be as Fischer and the applicant are directed toward inventions with opposite modes of action.

For any of the above reasons, including the assertion of unexpected results, the combination of Tisa-Bostedt and Fischer does not establish that the applicants' invention is *prima facie* obvious.

B. Claims 1-3 and 5 were rejected as allegedly being anticipated over Tavares et al. (WO 02/087482 - "Tavares") in view of Cote et al. (U.S. Patent Application Publication 2009-0209571 - "Cote") and Nielsen (WO 98/01167).

Applicants note that this rejection is reduced to Tavares in view of Nielsen as Cote does not qualify as prior art and does not support the Examiner's assertion that fentanyl is an opioid analgesic of from the phenanthrene group.

Like Tisa-Bostedt, Tavares was apparently relied upon for a teaching of fentanyl in a transdermal delivery system, but Tavares (and Nielsen) does not appear to have been considered as a whole and is so far removed from the applicants' invention, it is unclear why the claims were either not allowed or permitted to proceed to the BPAI.

The Office Action acknowledges that Tavares does not teach styrene-butadiene-styrene block copolymer or aloe. However, this is not the only difference between Tavares and the claimed invention.

First, as noted above with Tisa-Bostedt, fentanyl is not the same as or an obvious variant of buprenorphine; as Nielsen is relied upon to address the missing element of styrene-butadiene-styrene block copolymer or aloe, the combination of Tavares and Nielsen does not render the applicants' claimed invention to be obvious for this reason alone.

Second, given that the restriction requirement held that the selection of styrene-butadiene-styrene block copolymer as the adhesive represented a patentably distinct invention, there is no basis for obviousness on this element.

Third, Nielsen ***teaches away*** from the use of aloe as a skin penetrant. When considering Nielsen as a whole, it is clear that Nielsen is trying to achieve the ***exact opposite*** of what Tavares seeks to accomplish, i.e. rather than enhancing the penetration of fentanyl (which is the wrong opioid in any event), Nielsen surprisingly found that "…when adding Aloe vera to an adhesive agent for use in appliances to be used in connection with ***collection of exudates or excretions from a body***, a better protection of the skin against the aggressive action of excretions from the body is achieved." (see Brief Description of the Invention)

Moreover, as noted above in Fischer the behavior of a penetration enhancer is strongly dependent on the drug; neither Tavares not Nielsen show that the use of aloe was suitable for buprenorphine for transdermal delivery. In fact, neither fentanyl nor buprenorphine is even mentioned in the teachings of Nielsen.

For any of the above reasons, including the assertion of unexpected results, the combination of Tavares and Nielsen does not establish that the applicants' invention is *prima facie* obvious.

C. Claims 1-3, 5, 12-22 and 25-27 were rejected as allegedly being anticipated over Tavares et al. (WO 02/087482 - "Tavares") in view of Cote et al. (U.S. Patent Application Publication 2009-0209571 - "Cote") and Nielsen (WO 98/01167) and further in view of Fischer et al. (U.S. Patent 6,455,066 - "Fischer")

Applicants note that this rejection is reduced to Tavares in view of Nielsen and Fischer as Cote does not qualify as prior art and does not support the Examiner's assertion that fentanyl is an opioid analgesic of from the phenanthrene group.

In the interest of brevity, the applicants note that their arguments with respect to Tavares and Nielsen made above in section B. is equally applicable here and that the applicants arguments against the use of Fischer in section A. is also applicable here.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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